286100

STIC-ILL

From: Meller, Michael
Sent: Tuesday, March 07, 2000 1:26 PM
T : STIC-ILL
Subject: References

Art Unit- 1651
Room 10B13

1. Koido et al., Nippon Ika Daigaku Zasshi, 1997, 64(1), 9-15.

2. Dodosz et al., Hepato-Gastroenterology, 1991, 38(2), 139-142.

3. Okada et al., J. Int. Med. Res., 1991, 19(4), 348-350.

4. Okada et al., J. Int. Med. Res., 1991, 19(3), 234-236.

9131027

00030766?

Beneficial Effect of Therapeutic Infusion of Nafamostat Mesilate (FUT-175) on Hemodynamics in Experimental Acute Pancreatitis

M. Dobosz, Z. Śledziński, P. Juszkiewicz, A. Babicki, A. Stanek, Z. Wajda, [1]A. Basiński

Second Department of General Surgery, [1]Department of Anesthesiology, Medical Academy in Gdańsk, Poland

Summary

Acute pancreatitis was induced in 13 anesthetized dogs by retrograde injection of bile mixed with trypsin into the pancreatic duct. Six animals were treated with intravenous infusion of new synthetic antiprotease, Nafamostat Mesilate, at a dose of 1 mg/kg/h. Four out of seven untreated animals died during the experiment. All the treated dogs survived. Hemodynamic data were regularly monitored during a ten-hour observation period. Cardiac output, mean arterial pressure and left ventricular stroke volume decreased rapidly in the untreated animals. An increase in systemic vascular resistance and pulmonary vascular resistance was observed in dogs without treatment. Nafamostat Mesilate given as therapy significantly improved the hemodynamic parameters, and prevented the animals from developing shock. The study demonstrates an advantageous influence of synthetic antiprotease Nafamostat Mesilate on the course of acute experimental pancreatitis.

Key words

Acute pancreatitis – Antiprotease – Nafamostat Mesilate – Hemodynamics

Introduction

Active forms of pancreatic proteases are believed to play a crucial role in the pathogenesis of acute pancreatitis (1, 2, 3). Thus, antiproteolytic therapy could be of value in the treatment and prevention of the disturbances that occur during acute pancreatitis. Aprotinin, introduced into the therapeutic concept in 1954, does not seem to have had any clearly demonstrable therapeutic effect (1). A new Japanese synthetic antiprotease, Gabexate Mesilate (FOY), recently introduced in some hospitals (5, 6, 7), seems to be a promising drug in the treatment of acute pancreatitis, although the clinical results are still unclear and need further investigation.

Hepato-Gastroenterol. 38 (1991) 139–142

FUT-175, Nafamostat Mesilate, is another new synthetic protease inhibiting agent discovered by Japanese scientists. Recent investigations show a strong inhibitory effect of FUT-175 on serine protease both "in vitro" and "in vivo" (3, 8, 9), and suggest that Nafamostat Mesilate might be clinically useful in the treatment of acute pancreatitis. The aim of this study was to investigate the effects of FUT-175 on hemodynamic parameters within the framework of experimental acute pancreatitis.

Materials and methods

Eighteen male mongrel dogs weighing 14–22 kg were initially anesthetized with intramuscular ketamine hydrochloride (10 mg/kg Ketalar, Park and Davis). Supplementary doses of pentobarbital sodium were administered intravenously as required. After tracheal intubation, a catheter for monitoring arterial blood pressure was introduced into the femoral artery. The next catheter was introduced into the femoral vein for blood sampling and the administration of medicaments. A flow-directed Swan-Ganz thermodilution catheter (Model 93–132–5F) was floated into the pulmonary artery through the other femoral vein. The position of the Swan-Ganz catheter was confirmed by measuring the pressures during passage through the right heart circulation: vena cava, right atrium, right ventricle and pulmonary artery. Arterial, central venous and pulmonary arterial pressure were recorded hourly throughout the experiment, using a pressure transducer (Model P 23Db Gould) and a Sirecust recorder (Model B S1). Cardiac output determinations were obtained with the thermodilution technique, using a cardiac output computer (Tomel, Model COC–2).

The animals were divided into three groups. Group A: Five dogs underwent laparotomy and duodenotomy only. Group B: After laparotomy and duodenotomy in seven dogs, the pancreatic duct was cannulated and acute pancreatitis induced by injection of 10 ml of bile admixed with 25 mg of trypsin (Serva) and incubated for 24 hours at a temperature of 37 °C. The mixture was administered over a period of 5 minutes at a pressure of 70 cm H_2O. All the animals of group A and B were given 50 ml of isotonic saline during the experiment. Group C: After induction of acute pancreatitis, the animals were given continuous intravenous infusion of Nafamostat Mesilate (Tori and Co., Ltd) at a dose of 1 mg/kg/h mixed with 50 ml of isotonic glucose. Administration of FUT-175 – given by an automatic pump – started 30 minutes after the induction of acute pancreatitis, and lasted five hours.

All the animals were observed over a period of ten hours. Hemodynamic parameters: cardiac output (CO), mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), pulmonary arterial pressure (PAP) and pulmonary wedge pressure (PWP) were monitored every hour. The calculation of systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and left ventricular stroke volume (LVSV) were estimated in accordance with the usual formulae (15).

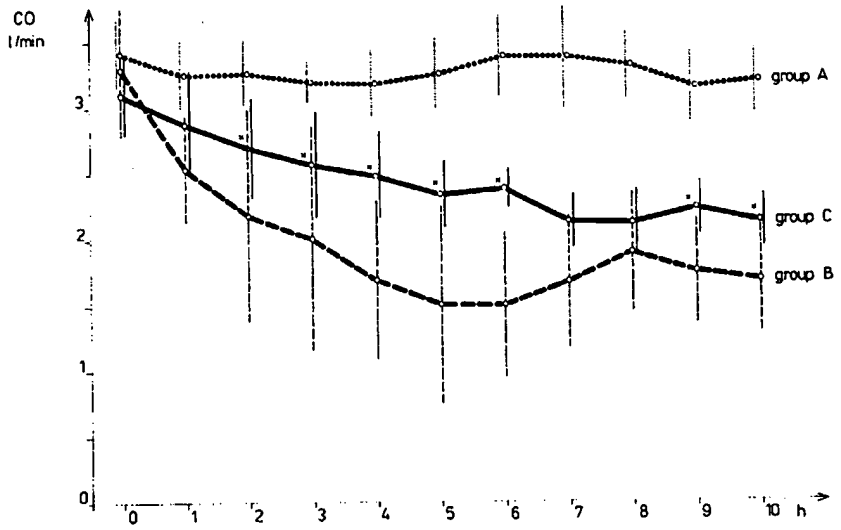

Fig. 1 Cardiac output in experimental acute pancreatitis. Group A (n = 5) – control. Group B (n = 7) – acute pancreatitis without treatment. Group C (n = 6) – acute pancreatitis treated with FUT-175. Mean values ± SD; $P < 0.05$ as compared with corresponding values of group B

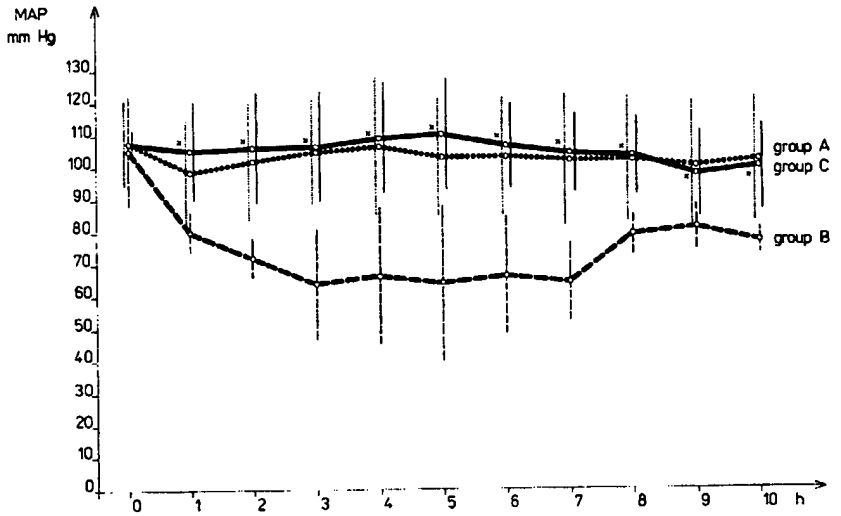

Fig. 2 Mean arterial pressure in groups A, B, C. Mean values ± SD; $P < 0.05$ as compared with corresponding values of group B

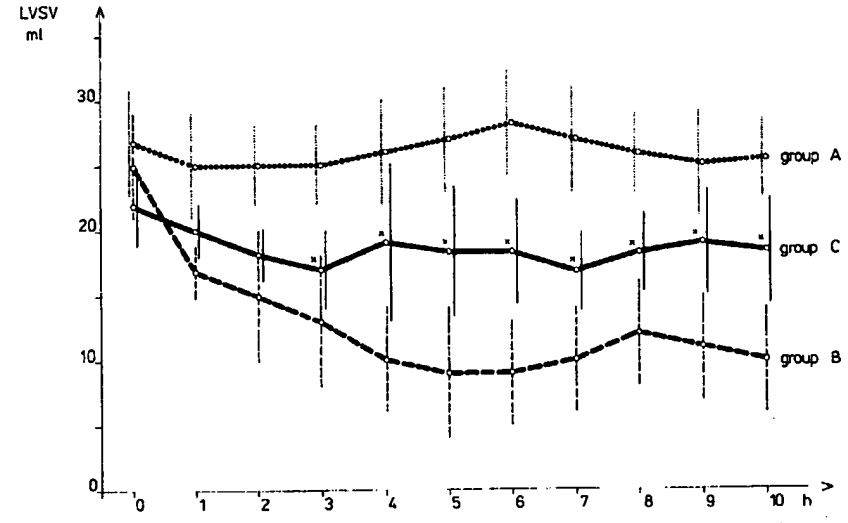

Fig. 3 Left ventricular stroke volume in groups A, B, C. Mean values ± SD; $P < 0.05$ as compared with corresponding values of the group B

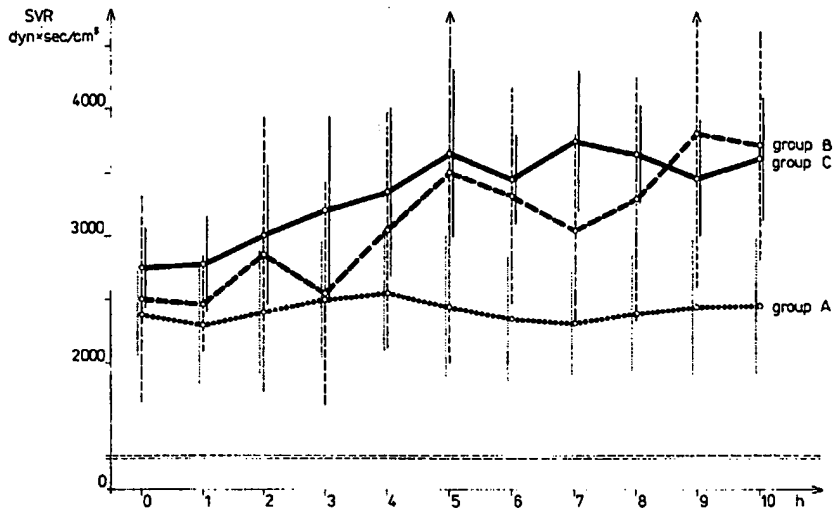

Fig. 4 Systemic vascular resistance in groups A, B, C. No statistical significance between groups A and C

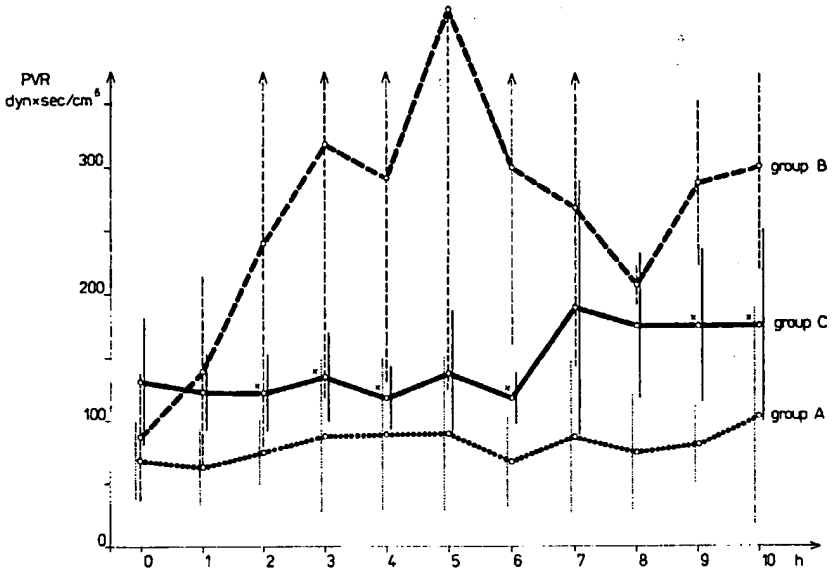

Fig. 5 Pulmonary vascular resistance in groups A, B, C. Mean values ± SD; $P < 0.05$ as compared with corresponding values of group B

The data were analysed statistically using Student's T test, and p values < 0.05 were considered significant.

Results

Acute hemorrhagic pancreatitis, confirmed by histological examination developed in all the animals in groups B and C. The morphological changes – which were less pronounced in the animals treated with FUT-175 – included necrosis of the pancreas and accumulation of hemorrhagic fluid within the peritoneal cavity. Four dogs (57%) in group B died during the experiment (after the fifth, sixth, seventh and eighth hours). All the animals in group C survived. A rapid significant decrease in CO, MAP and LVSV was observed in the untreated animals in group B. This was not seen in the animals treated with Nafamostat Mesilate (Fig. 1, 2, 3). PVR rose in dogs not receiving treatment, and to a smaller extent in the animals receiving FUT-175 (Fig. 5). A slight, statistically non-significant increase in SVR was observed in both group B and C (Fig. 4).

Discussion

Experimental and clinical studies indicate that severe acute pancreatitis causes the inflammed pancreas to liberate active enzymes and toxins into the peritoneal cavity, the retroperitoneal space and the general circulation (1, 11). The activation of the kinin system, an increase in prostaglandins, and the formation of a substance that increases vascular permeability, may be important in the pathogenesis of the shock syndrome (2). Trypsin, being a potent unspecific protease capable of activating other enzymes (2), can release bradykinin and induce C_3 and C_5 activation, and may have a significant role in the development of ARDS (1). Finally, phospholipase A_2, in particular, has been implicated as an agent that causes direct injury to the pulmonary capillary endothelium, aggravating the respiratory insufficiency (12).

Our present study confirms hemodynamic consequences in experimental pancreatitis (2, 13), although they are different from hemodynamic data obtained in patients under clinical conditions (10, 11). Untreated animals

developed progressive circulatory insufficiency as reflected in the decrease in CO, MAP and LVSV. A significant rise in pulmonary vascular resistance may indicate the development of ARDS in the early stage of acute pancreatitis (14).

The circulatory changes mentioned above were significantly less pronounced in the group receiving Nafamostat Mesilate as therapy. Thanks to its strong inhibitory effect (100 times stronger than other antiproteases) (9), and wide spectrum as a protease inhibiting agent (3, 8), FUT-175 protected all the treated animals from severe hemodynamic disturbances. A specific inhibitory action of FUT-175 on the kinin-kallikrein system (3, 8) reduces membrane permeability and prevents hypovolemia and shock.

The other complications connected with coagulation and fibrinolysis in acute pancreatitis could be prevented by FUT-175 thanks its inhibitory effect on thrombin and plasmin (3, 8).

On the other hand, apart from preventing the formation of cytotoxic lysolecithin in the pancreas (6), the inhibition of phospholipase A_2 could protect pulmonary surfactant from enzymic degradation and thus prevent the development of ARDS (12). Similarly, the inhibition of the complement system by FUT-175 (3, 8) could, in theory, also afford protection from pulmonary consequences in acute pancreatitis (1).

Finally, Nafamostat Mesilate could be considered clinically useful in the treatment of acute pancreatitis.

References

1 *Thomas, P. D.:* Acute pancreatitis. Anaesth. Intens. Care 13 (1985) 249–257

2 *Ruud, T. E., A. O. Aasen, J. Pillgram-Larsen, J. O. Stadaas:* Protease inhibitor infusion improves survival rate and hemodynamics in experimental pancreatic shock. First Vienna Shock Forum, Part A: Pathophysiological Role of Mediators and Mediator Inhibitors in Shock (1987) 193–201

3 *Iwaki, M., Y. Ino, A. Motoyoshi, M. Ozeki, T. Sato, M. Kurumi, T. Aoyama:* Pharmacological studies of FUT-175, Nafamostat Mesilate, V. Effects on the pancreatic enzymes and experimental acute pancreatitis in rats. Japan J. Pharmacol. 41 (1986) 155–162

4 *Tykka, H. T., E. J. Vaittinen, K. L. Mahlberg, J. E. Railo, P. J. Pantzar, S. Sarna, T. Tallberg:* A randomized double-blind study using $CaNa_2$ EDTA, a phospholipase A_2 inhibitor in the management of human acute pancreatitis. Scand. J. Gastroenterol. 20 (1985) 5–12

5 *Kahle, M., R. D. Filler, K. H. Muhrer, P. Hild:* Therapie der akuten Pankreatitis mit dem Enzyminhibitor Gabexat mesilat. Münch. med. Wschr. 128, 44 (1986) 756–758

6 *Freise, J., F. W. Schmidt, P. Mogerstedt, K. Schmid:* Gabexate Mesilate and Camostate: New inhibitors of phospholipase A_2 and their influence on the alpha-amylase activity in serum of patients with acute pancreatitis. Clin. Bioch. 18 (1985) 224–229

7 *Freise, J., P. Melzer, F. W. Schmidt, L. Horbach:* Gabexat mesilat in der Behandlung der akuten Pankreatitis Ergebnisse der hannoverschen multizentrischen Doppelblindstudie mit 50 Patienten. Z. Gastroenterologie 24 (1986) 200–211

8 *Aoyama, T., Y. Ino, M. Ozeki, M. Oda, T. Sato, Y. Koshiyama, S. Suzuki, M. Fujita:* Pharmacological studies of FUT-175, Nafamostat Mesilate, I. Inhibition of protease activity in in vitro and in vivo experiments. Japan J. Pharmacol. 35 (1984) 203–227

9 *Satake, K., J. Koh, H. Nishiwaki, K. Umeyama:* Toxic products in hemorhagic ascitic fluid generated during experimental acute hemorhagic pancreatitis in dogs and a treatment which reduces their effect. Digestion 32 (1985) 99–105

10 *Bradley, E. L., J. R. Hall, J. Lutz, L. Hammer, O. Lattouf:* Hemodynamic consequences of severe pancreatitis. Ann. Surg. 198, 2 (1983) 130–133

11 *Beger, H. G., R. Bittner, M. Büchler, W. Hess, J. E. Schmitz:* Hemodynamic data pattern in patients with acute pancreatitis. Gastroenterology 90 (1986) 74–79

12 *Guice, K. S., K. T. Oldham, R. R. Wolfe, R. H. Simon:* Lung injury in acute pancreatitis. Primary inhibition of phospholipid synthesis. Am. J. Surg. 153 (1987) 54–61

13 *Martin, D. T., S. M. Steinberg, R. Kopolovic, L. C. Carey, C. T. Cloutier:* Crystalloid versus colloid resuscitation in experimental hemorrhagic pancreatitis. Surg. Gynecol. Obstet. 159 (1984) 445–449

14 *Shoemaker, W. C., P. L. Appel:* Pathophysiology of adult respiratory distress syndrome after sepsis and surgical operations. Crit. Care. Med. 13, 3 (1985) 166–172

Marek Dobosz, M. D.

Second Department of General Surgery
Medical Academy in Gdańsk
Kieturakisa 1 street, PL-80–742 Gdansk, Poland